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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,542	10/07/2004	Neil Lee Spector	PU4725USW	8482

23347 7590 06/04/2008

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
06/04/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/510,542	SPECTOR ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 5 and 25 are presented for examination

Applicants' amendment filed 3/4/2008 has been received and entered into the application. Accordingly, claim 5 has been amended.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Response to Arguments

Applicant's arguments filed 3/4/2008 have been fully considered but they are not persuasive. Applicants argue that the present application demonstrates that the particular combination of compounds recited in claims 5 and 25 as amended has unexpected results. In support of this argument, Applicants point to Figures 4 and 5 as demonstrating that the claimed combination shows increased HB4a-ras cell mortality (Figure 4) and apoptosis (Figure 5) in comparison to either compound alone. Regarding the results shown in Figures 4 and 5, the Examiner notes that very specific nature of the testing conditions compared to the instant claims and teachings of the prior art. For example, the cells in Figures 4 and 5 are HB4a-ras cells (*i.e.*, "normal" mammary lumenal epithelial cells transfected with Ha-(Val 12)-ras, **not** breast cancer cells. Further, the examples in Figures 4 and 5 are limited to specific doses (10 μM) and times of exposure (72 hours) and are carried out *in vitro*, whereas the claims recite any "therapeutically effective amounts" to mammals (*i.e.*, *in vivo*), and place no limitation on the time period of

exposure to the agents. Further still, nowhere do the examples of Figures 4 and 5 administer the monohydrate ditosylate salt of the compound of Formula (III) as recited in claim 25. As such, it is not seen by the Examiner that the results of *in vitro* administration of a combination of 10 μM GW2016 and 10 μM GW5074 to HB4a-ras cells is commensurate in scope with "treating" breast cancer in a mammal with any therapeutically effective amounts of GW2016 and GW5074 as instantly claimed and suggested by the prior art.

Accordingly, the rejection of claims 5 and 25 is maintained for the reasons of record and as reiterated below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 5 and 25 are again rejected under 35 U.S.C. § 103(a) as being unpatentable over **Carter *et al.*** (WO 99/35146; Published July 15, 1999) in view of **Dickerson *et al.*** (U.S. Patent No. 6,268,391; Issued July 31, 2001).

Instant claim 5 recites a method of treating breast cancer comprising administering the compound of formula (III) and the cRaf-1 inhibitor depicted in the claim (i.e., 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-iodo-1,3- dihydro-indol-2-one).

Carter *et al.* disclose methods of treating human malignancies, including breast, gastric, head and neck, and pancreatic tumors, especially those driven by EGF-R or erbB-2, comprising administering compounds of formula (I) (page 3, lines 4-12; page 3, line 24 to page 13, line 26; page 50, lines 10-17). Preferred compounds of the invention include the instantly claimed compound (page 37, lines 33-34 and page 100, Example 29). Salts of the compounds disclosed in Carter *et al.* are taught at page 40, lines 5-14 and reasonably suggest the instantly claimed monohydrate ditosylate salt of the compound of formula (III) as instantly claimed. Carter *et al.* suggest that the compounds of the invention "and their salts and solvates" may be employed alone or in combination with other therapeutic agents for the treatment of cancer (page 54, lines 8-10). For anticancer therapy, combination with other chemotherapeutic, hormonal or antibody agents is envisaged (*id.* at lines 10-11). The reference thus provides explicit motivation to combine the instantly claimed compound with other chemotherapeutic agents for the treatment of cancer. The instantly claimed compound of formula (III) was shown to effectively inhibit the growth of HB4a (erbB2) mammary cells, BT474 breast cancer cells, HN5 head and neck cancer cells and N87 gastric cancer cells (page 110, Table 2, Example 29). HB4a mammary cells transfected with H-ras cDNA were not inhibited by the claimed compound (*id.*).

However, Dickerson *et al.* disclose compounds that can be used in the treatment of disorders mediated by cRaf1 kinase (Abstract). cRaf1 kinase is deregulated by events that are common in human cancer. For example, ras genes are mutated with the following frequencies in the following representative primary tumors: lung, 30%; colon, 50%; pancreatic, 90% (col. 2, lines 53-58). cRaf1 is also activated by deregulation of tyrosine kinases including, cSrc, ErbB2, EGFR and bcr/abl. These events are associated with breast, colon, and lung carcinomas (*id.* at lines 60-63). Dickerson *et al.* thus provide compounds (col. 4, line 1 to col. 23, line 47) for the treatment of human malignancies, including breast, pancreatic and gastric cancer (col. 3, lines 35-47 and col. 23, lines 49-60). Combination therapy with other known anti-tumor therapies for more effective treatment of such tumors is disclosed (col. 24, lines 36-40). The reference thus provides the motivation to combine an inhibitor of cRaf1 with other anti-tumor agents for the treatment of cancer. The effectiveness of representative compounds of the invention in inhibiting colon, pancreatic, breast and prostate cancer cell growth is demonstrated in Table 4 (col. 102). With regard to the specific cRaf-1 inhibitor recited in the instant claims, Dickerson et al. explicitly exemplify this compound as a useful compound of the invention (see col. 18, lines 1-10; Table 1A, Compound 79; col. 58, lines 65-66).

The instantly claimed methods of treating breast cancer would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The instantly claimed compound of formula (III) and cRaf-1 inhibitors were both known in the art to inhibit the *in vitro* growth of the same cancer cell lines (*e.g.*, breast and pancreatic). Further, Carter *et al.* and Dickerson *et al.* both suggest and provide the skilled artisan with the motivation to combine erbB2 inhibitors (such as a compound of formula (III)) and cRaf-1 inhibitors for the

treatment of cancer. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed *supra*). The natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption.

Further, erbB2 inhibitors and cRaf-1 inhibitors have different mechanisms of action and cRaf-1 is activated by deregulation of tyrosine kinases including, cSrc, ErbB2, EGFR and bcr/abl (Dickerson *et al*. at col. 2, lines 60-63). As such, the skilled artisan would have been imbued with at least a reasonable expectation that a combination of the compound of formula (III) and a cRaf-1 inhibitor would be an effective treatment of breast cancer.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
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